TITLE PAGE

Title: Improvements over time in short-term mortality following myocardial infarction in the D:A:D Study

RUNNING HEAD: Short-term mortality after MI

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Authors:

Camilla Ingrid HATLEBERG[1], Lene RYOM[1], Wafaa EL-SADR[2], Colette SMITH[3], Rainer WEBER[4], Peter REISS[5], Eric FONTAS[6], Francois DABIS[7], Matthew LAW[8], Antonella d'Arminio MONFORTE[9], Stephane De WIT[10], Amanda MOCROFT[3], Andrew PHILLIPS[3], Jens D. LUNDGREN[1] and Caroline SABIN[3] for the D:A:D Study Group

1. CHIP, Department of Infectious Diseases, Section 2100, Rigshospitalet, University of Copenhagen, Denmark

2. ICAP-Columbia University and Harlem Hospital, New York, United States

3. Research Department of Infection and Population Health, UCL, London, United Kingdom

4. Division of Infectious Diseases and Hospital Epidemiology, University Hospital Zurich, University of Zurich, Switzerland

5. Academic Medical Center, Dept. of Global Health and Div. of Infectious Diseases, University of Amsterdam, and HIV Monitoring Foundation, Amsterdam, The Netherlands

6. Department of Public Health, Nice University Hospital, Nice, France

7. Université de Bordeaux, ISPED, Centre INSERM U897-Epidemiologie-Biostatistique, Bordeaux, France

8. The Kirby Institute, UNSW Australia, Sydney, Australia

9. Dipartimento di Scienze della Salute, Clinica di Malattie Infettive e Tropicali, Azienda Ospedaliera-Polo Universitario San Paolo, Milan Italy

10. Division of Infectious Diseases, Saint Pierre University Hospital, Université Libre de Bruxelles, Brussels, Belgium

CORRESPONDING AUTHOR AND REPRINTS

Camilla Ingrid Hatleberg, MD

CHIP, Dept. of Infectious Diseases, Section 2100, Rigshospitalet, University of Copenhagen

Blegdamsvej 9,

DK-2100 Copenhagen

Tel: + 45 35 45 57 70/ Fax: +45 35 45 57 57/ email: Camilla.hatleberg@regionh.dk

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ABSTRACT (249, max 250 words)

Objective: Few studies have described mortality and clinical outcomes after myocardial infarction (MI) in the HIV-positive population. This study evaluated changes in short-term mortality after MI in HIV-positive individuals in the D:A:D Study, and investigated possible reasons for any changes seen.

Design: Prospective cohort study.

Methods: Demographic, cardiovascular disease (CVD)/HIV-related characteristics and CVD-related interventions (invasive cardiovascular procedures and drug interventions) were summarised at the time of and following an MI. Associations between calendar year and mortality in the first month after MI were identified using logistic regression with adjustment for confounders, including interventions received in the first month after MI.

Results: 1008 HIV-positive individuals experiencing an MI over the period 1999-2014 were included. The absolute number of MIs decreased from 214 (1999-2002) to 154 (2011-2014). Whilst the CVD risk profile remained high over time, the HIV status improved. The use of CVD-related interventions after MI appeared to increase over time. The proportion of individuals who died in the first month after MI dropped from 26.6% in 1999-2002 to 8.4% in 2011-2014. Later calendar year was associated with decreased short-term mortality; this effect was attenuated after adjusting for CVD-related interventions received in the first month after MI (odds ratio changed from 0.88 [95% confidence interval 0.83, 0.93] to 0.97 [0.91, 1.02]).

Conclusions: Improvements in short-term survival after MI appear to be largely driven by improved medical management of CVD risk in HIV-positive individuals after MI.

Efforts are still needed to treat CVD risk factors and increase access to CVD-related interventions.

Key words: Cardiovascular disease, myocardial infarction, HIV infection, cardiovascular interventions, mortality

INTRODUCTION

The mortality rate after a first myocardial infarction (MI) has declined in individuals of all ages in the general population over the past 25 years[1] [2]. This improvement is mainly attributable to better management of cardiovascular disease (CVD) risk factors and the increased use of recommended medical therapies and invasive cardiovascular procedures (ICPs)[1] [2]. It is well documented that HIV-positive persons have a higher risk of CVD; multiple factors, not all of which are fully explained, may contribute to development of atherosclerosis in this population. The prevalence of many traditional CVD risk factors (e. g smoking, dyslipidemia) is higher in HIV-positive persons than in the general population[3] [4]. Although some studies have reported an improvement over the years[5], earlier findings from the D:A:D Study demonstrated that the CVD risk profile of individuals living with human immunodeficiency virus (HIV) in the cohort generally worsened from 1999-2006[6]. In addition, exposure to some antiretroviral (ARV) drugs has been shown to be associated with an increased risk of MI[7] [8] [9] [10] [11] [12]. Furthermore, the increased CVD risk noted in HIV-positive individuals may also be related to HIV-related chronic inflammation and immunosuppression[10] [8] [13] [14] [15] [16]. Whilst incidence rates of MI in the HIV-positive population are higher than in the HIV-negative population[17] [18] [13], there has been a decrease in the rate over time in the D:A:D Study, likely as a result of a more aggressive targeted approach to the management of CVD risk factors[6]. Recent studies have also reported a decreasing trend to the excess MI risk in HIV-positive people compared to the general population in later years[19] [20].

Examples of independent predictors of increased mortality after MI in the general population include older age, male gender, in-hospital cardiac complications and no ICP after MIs[21]. Previous findings have shown that HIV-positive individuals admitted for acute coronary syndromes faced a substantial short-term risk of death and an increased risk of coronary

revascularization, recurrent MI[22] and all-cause mortality one year after MI[23]. However, few studies have described mortality and clinical outcomes after MI in the HIV-positive population and changes in such outcomes over time. The primary objective of this study was to investigate changes over time in short-term mortality after MI in HIV-positive participants in the D:A:D Study, and possible explanations for any changes seen.

MATERIAL AND METHODS

The D:A:D (Data on Adverse events of antiretroviral Drugs) study is a large, prospective observational cohort study which follows >49,000 HIV-positive persons from 11 collaborating cohorts in Europe, USA and Australia; to date, these persons have contributed >350,000 person-years of follow-up. The primary aim is to investigate associations between the use of ARV drugs and risk of CVD[7]. The data include information on socio-demographic factors, acquired immunodeficiency syndrome (AIDS) events, CD4 count, HIV viral load (VL), other laboratory results, ARV-regimen/ treatment history and CVD risk factors/ treatments. Data are reported to the D:A:D coordinating centre as anonymous, computerized case report files and then merged into a standardized central dataset. All cases of MI are validated centrally using criteria from the WHO MONICA Study[24] and classified using a Dundee score[24] as definite, possible or unclassifiable and further distinguished into non-fatal and fatal events. In addition, ICPs (coronary artery bypass graft (CABG), carotid angioplasty (ANG) and carotid endarterectomy (END)) are reported. Information on causes of death is collected using a designated Coding of Causes of Death in HIV (CoDe) form (www.chip.dk/code)[25]. This analysis was conducted in accordance with the Declaration of Helsinki and approved by national ethical committee where necessary.

Statistical methods

All individuals experiencing an MI during prospective follow-up from study initiation in 1999 to February 1st, 2014 were identified. Demographic, HIV/CVD-related characteristics and the use of CVD interventions (ICPs, receipt of anti-platelets, angiotensin-converting enzyme inhibitors (ACEIs), other anti-hypertensives (including beta-blockers) and lipid-lowering drugs (LLDs)) were described at the time of the MI and over the follow-up period. Mortality after MI was described using Kaplan-Meier methods, with follow-up on individuals

who remained alive being right-censored six months after their last clinic visit or on 1st February 2014, whichever was earlier. Only the first MI that occurred over follow-up was considered for each individual (although some individuals had experienced their first ever MI prior to enrolment in the study).

Factors associated with overall mortality and mortality from the first month after MI onwards were identified using Cox Proportional Hazards regression models. Factors (measured at the time of MI) that were considered for inclusion in these models were: age, gender, mode of HIV acquisition, ethnicity, cohort, calendar year of MI, current/cumulative exposure to ARVs, prior AIDS diagnosis, CD4 count, VL, smoking status, body mass index, family history of CVD, hypertension (systolic blood pressure >140 mm Hg and/or diastolic blood pressure >90 mm Hg and/or on ACEIs or other anti-hypertensives[26]), dyslipidaemia (total cholesterol (TC) $\geq$6.2 mmol/L or hyperdensity lipoprotein cholesterol (HDL-C) $\leq$0.9 mmol/L or TC:HDL-C ratio $\geq$6.5 or receipt of LLDs[26]), prior diabetes, prior stroke (both centrally validated), prior MI and Framingham risk score. Factors that were associated with mortality in univariable analyses ($p<0.1$) were considered for inclusion in the multivariable model with a stepwise selection procedure used to identify the factors that would be retained in the model. The resulting model was then further adjusted for interventions received in the first month after MI.

Factors associated with short-term mortality (deaths occurring within the first 31 days after MI) were identified using unadjusted/adjusted logistic regression models with potential confounders selected as described above. All models included calendar year as this was our exposure of interest; analyses were restricted to individuals with at least one month of follow-up (or those who had died within the first month) to avoid introducing bias due to variable

follow-up times over this first month. Analyses were performed separately for CVD/non-CVD related deaths and stratified by calendar period.

RESULTS

Characteristics of individuals at time of an MI

1008 D:A:D participants experienced an MI over the period 1999-2014. The majority were men (90.8%), the median (interquartile range [IQR]) age at the time of MI was 51 [44, 58] years, and 55.9% were of white ethnicity. The most prevalent CVD risk factors seen were dyslipidemia (66.6%), current smoking (53.3%) and hypertension (42.5%); around 1 in 3 individuals with an MI were known to be receiving LLDs (35.5%) and 1 in 4 (26.4%) anti-hypertensives. At the time of MI, 90.4% of the individuals were on ARV treatment with only 2.7% being ARV-naïve (the remaining 6.9% had previously received ARV treatment). The median [IQR] 10-year predicted CVD risk (based on the Framingham score, available in 82.1% of those with an MI) was 14.1% [8.9%, 20.7%]; 58.2% of the individuals with an available score had a moderate to high predicted risk of >10% (Table 1).

The number of MIs in each year is shown in Table 1. The proportion of MIs in each year that was classified as definite MIs was stable (58.9% in 1999-2002 to 60.4% in 2011-2014). There were some changes in the characteristics of individuals that experienced an MI over the same period; the median age increased from 48 years to 54 years, the proportion of current smokers increased from 49.5% to 54.6%, and there were increases in the proportions of individuals who had dyslipidemia, hypertension and a moderate/high Framingham risk score. In more recent years, a higher proportion of individuals were on ARV therapy, had a suppressed VL and a higher CD4 count (Table 1).

Interventions at or after time of MI

Overall, 581 (57.6%) of the study participants underwent an angioplasty, 87 (8.6%) a CABG and 7 (0.7%) an endarterectomy following their MI, with 620 (61.5%) of participants undergoing at least one ICP after MI. Just under two-thirds, 370 (59.7%) of the ICPs were carried out on the same day as the MI, 168 (27.1%) were carried out within the first 31 days and the remaining 82 (13.2%) were carried out more than 31 days after MI. LLDs were initiated after MI in 397 of 650 participants (61.1%) who were not already receiving them, with 254 (63.9%) of these initiating LLDs within the first month after MI; anti-platelets, ACEIs and anti-hypertensives were initiated in 477 of 758 participants (62.9%) (362 (75.9%) within the first month after MI), 354 of 810 participants (43.7%) (202 (57.1%) within the first month after MI) and 399 of 742 participants (53.8%) (265 (66.5%) within the first month after MI), respectively. In general, there seemed to be an increasing trend over time in the use of medical interventions prior to MI and in all interventions after MI (Figure 1).

Causes of death following MI

Over a median [IQR] follow-up time of 42.7 [9.6, 84.0] months after their MI, 117 of the 1008 HIV-positive individuals (11.6%) experienced a further MI and 339 (33.6%) died.

Of the deaths that occurred, 145 (42.8% of deaths, 14.4% of all individuals) were on the same day as the MI, 37 (10.7% of deaths, 3.7% of all individuals) were within the first month after the MI, and 157 (46.3% of deaths, 15.6% of all individuals) were more than 31 days after MI. The proportion of deaths that were due to CVD varied according to the timing of the death relative to the MI: 129 (89%) and 33 (87.1%) of deaths that occurred on the same day as the MI or within the first month after MI were due to CVD respectively, whereas only 59 (37.6%) of deaths that occurred >31 days after MI were due to CVD (Figure 2a). In total, 182 deaths occurred in the first month after MI yielding an overall short-term mortality rate of

18.1%; this rate dropped from 26.6% in 1999-2002 to 8.4% in 2011-2014. The overall proportion of individuals dying from any CVD dropped from 72.6% in 1999-2002 to 40.9% in 2011-2014, whereas the proportion of individuals dying from causes other than CVD following their MI increased over the same period; major contributing causes being HIV/AIDS, non-AIDS cancers, bacterial infections, lung disease and unknown causes (Figure 2b).

Factors associated with overall mortality following MI

In unadjusted proportional hazards regression models, factors associated with increased mortality were: older age; injection drug use (IDU) mode of HIV acquisition; black African ethnicity; prior AIDS; higher VL; diabetes; prior MI; and prior stroke. Higher CD4 count, later calendar year of MI and family history of CVD were all associated with decreased mortality (data not shown). In a multivariable model, all these factors remained independently associated with mortality except black African ethnicity, prior AIDS and higher VL.

In order to investigate the potential impact of interventions received in the first month post-MI, the analysis was repeated after excluding individuals who did not survive or remain under follow-up beyond the first month. Factors remaining independently associated with mortality in this multivariable model were: older age; prior AIDS; higher VL; previous MI; diabetes; and later calendar year (Table 2). Additional adjustment for the interventions received in the first month had only minor effects on the associations between these factors and mortality, although it led to an attenuation of the calendar year association from hazard rate (HR) 0.95 [95% confidence interval (CI) 0.89, 1.00] per later year to 0.98 [95% CI 0.92, 1.04] per later year (Table 2). Of the interventions themselves, only the ICPs demonstrated a strong association with mortality in this model.

Factors associated with short-term mortality following MI

In unadjusted logistic regression models, the factors associated with an increased risk of short-term mortality were: IDU mode of HIV acquisition; black African ethnicity; prior AIDS; higher VL and prior stroke. A family history of CVD, higher CD4 count and later calendar year were associated with decreased risk of short-term mortality (data not shown). In a multivariable model excluding interventions during the first month after MI, IDU mode of HIV acquisition, higher CD4 count, family history of CVD and prior stroke continued to be associated with short-term mortality, and again there was a strong calendar year effect (Table 3). When including interventions received in the first month following MI, ICPs, LLDs and anti-platelets were significantly associated with decreased risk of short-term mortality, and this led to attenuations of the associations with prior stroke (from odds ratio (OR) 3.24 [95% CI 1.61, 6.53] to 2.08 [95% CI 0.90, 4.84]) and family history of CVD (from 0.46 [95% CI 0.25, 0.86] to 0.61 [95% CI 0.30, 1.24]). The calendar year effect was attenuated from 0.88 [95% CI 0.83, 0.93] to 0.97 [95% CI 0.91, 1.02] in this adjusted model (Table 3).

DISCUSSION

We observed an improvement in survival after MI in the D:A:D cohort over the last 15 years. Those who experienced an MI continued to be individuals with a high CVD risk profile, although their HIV-related health indicators improved. There was an increase in the use of interventions at the time of, and shortly after an MI, and we observed a reduction in the short-term mortality rate following MI. Predictors of decreased short-term mortality were higher CD4 count, family history of CVD, later year of MI and the receipt of anti-platelets, LLDs and ICPs. When adjusting for CVD interventions in the first month after MI, the calendar year effect on short term-mortality was attenuated, arguing that the observed change is mainly driven by the increased use of interventions in recent years.

Within the D:A:D Study, we have seen a gradual reduction in the risk of MI over time in line with findings from the general population[27], and in the present study, we observed some changes in the characteristics of individuals experiencing an MI. As previously documented[28], the key demographic characteristics in individuals at the time of MI were male gender and older age, and other CVD risk factors were dominated by modifiable factors, i.e. current smoking, hypertension and dyslipidemia. There were notable increases in the proportions of people with an MI who were known to have dyslipidemia and/or hypertension, and slight increases in the proportions of individuals with a moderate to high Framingham risk score. Most likely this reflects improved monitoring of lipids and blood pressure in the cohorts rather than any change over time in the risk conferred by these conditions, as well as increased awareness and monitoring of CVD risk and gradual aging of individuals in the cohort, respectively. These findings are consistent with earlier studies[6 15 29 30 31]. The proportion of individuals with an MI who were on ARV therapy with a suppressed VL increased, as did the median CD4 cell count. This improvement in HIV-related health indices

amongst participants in the study has probably contributed to the improved survival seen over the study period. The use of improved ARV drugs with fewer metabolic side effects in recent years may also partly explain the improved survival, although we did not specifically investigate this in our study.

The HIV-positive population has changed significantly over the last decade as HIV/AIDS-related morbidity and mortality rates have declined and other causes of death have become increasingly common[32 33 34]. The all-cause mortality rate in the D:A:D Study population fell from 17.5 /1000 person-years (PYRS) in 1999/2000 to 9.1 /1000 PYRS in 2009-2011; the leading causes of death being AIDS-and HIV-related causes, non-AIDS defining cancers, liver disease and CVD[32]. The crude CVD incidence mortality rate fell from 1.8 /1000 PYRS to 0.9 /1000 PYRS from 1999-2011[32]. In this analysis, nearly 90% of individuals who died within the first month after MI died of CVD-related causes. Athough the short-term mortality rates after MI dropped, our findings emphasise the importance of continued improvement of the management of CVD in HIV-positive individuals. The magnitude of the reduction in short-term mortality after MI over time in this study (26.6 % to 8.4%) is similar to the reductions seen in the general population over the last 15-20 years, although mortality is still higher in our study population compared to equally young HIV-negative individuals (< 65 years)[1].

The clear improvements in survival outcomes in our study, particularly short-term mortality in the month following MI, appeared to be largely driven by improved clinical management. The use of ICPs increased by 35% from 1999-2002 to 2011-2014 ; where ICPs were used, angioplasties in particular tended to be undertaken on the same day as the MI. In some studies, HIV-positive individuals have previously been found to have a higher rate of recurrent MIs and to more frequently undergo urgent angioplasties[18 28 35 36 37] . The

proportion of recurrent MIs in the study was 11.6%; which is higher compared to previous findings from the general population (8.9% in 2010)[38]. We were unable to systematically evaluate the type of MI and degree of vessel disease, but the relatively young median age of the study participants at the time of MI may indicate that a higher proportion may have had a ST-elevated myocardial infarction (STEMI), as an inverse relationship has been demonstrated in men in the general population between age and the likelihood of the MI being a STEMI[39]. A STEMI often require urgent invasive treatment, possibly partly explaining the increased use of ICPs seen, and the latter may also be explained by the improvement in HIV-related characteristics, increasing the eligibility of individuals to undergo ICPs than was the case in earlier years.

We reported an increasing trend in the use of certain drugs following MI over time; LLDs and anti-platelets were the drugs most frequently started in those not already on these medications, arguing that secondary medical prophylaxis of CVD seem to be somewhat improving. The effectiveness and quality of CVD drugs may have also improved in more recent years, possibly contributing to improved survival.

In our study, we found that the calendar year effect on decreased short-term mortality seemed to be mediated through the increased use of CVD interventions in recent years, as its effect was attenuated after adjusting for interventions received in the first month after MI. Adjustment for interventions did not influence the decreased short-term mortality risk associated with a higher CD4 count. Similarly, adjustment for interventions received in the first month after MI also resulted in an attenuation of the calendar effect on long-term mortality, again suggesting that this effect was mediated through the use of interventions. Adjusting for interventions in the first month following MI did, however, not influence the predictors of increased long-term mortality, whereas the associations between stroke, family

history of CVD and IDU mode of HIV acquisition and short-term mortality were weakened, suggesting also these associations to be partly influenced by the use of interventions.

One study previously demonstrated that HIV status influences long-term risk for adverse outcomes after MI by being an independent predictor for long-term risk of heart failure[40]. In our study, we were unable to assess the impact of HIV per se, but found that survival substantially improved in line with improvements in the CD4 count, which was an independent predictor for decreased short-term mortality. The current longer-term outcomes after MI need to be further explored in our study population.

Although we demonstrated that an increased number of HIV-positive individuals now receive invasive and medical interventions after MI, there is still a proportion of individuals surviving their MIs who do not appear to receive these interventions. One possible explanation is under- or delayed ascertainment of such interventions. However, findings from our annual monitoring process suggest that the number of missed clinical events in the D:A:D Study is very low. Complicating co-morbidities influencing the eligibility of a person to undergo ICPs, the type of MI, and differences in clinical practices at different medical centres may also play a role. Further, the use of drug interventions in those with HIV is often challenging given the possibility of drug-drug interactions with ARV drugs[6 41], which may limit CVD treatment options. Finally, previous findings have reported that there is a inverse relationship between in-hospital mortality after MI and the number of CVD risk factors present at the time of MI[42], indicating that low-risk individuals may therefore have other, as yet unidentified, factors which may contribute to progressive disease[42].

Some limitations to our study need to be acknowledged. The use of non-medical interventions (e.g dietary advice, advice on smoking cessation or exercise) is not captured systematically in the D:A:D Study, and may have contributed to improved survival. Further,

it is complicated to evaluate the effect of relatively infrequent interventions, such as the use of ICPs, in an observational cohort as analyses of these interventions are likely to be affected by time-varying confounding and standard analytical methods are likely to give biased estimates. Finally, we did not evaluate the status of interventions at time of any recurrent MI although these may also have changed over time.

CONCLUSION

In this study, we demonstrated improvements in short-term survival after MI in HIV-positive individuals, which appeared to be largely driven by increased use of drug interventions and ICPs. However, some individuals are still not receiving these interventions despite a high CVD risk profile. Our findings suggest that preventive measures need to be further explored, with targeted focusing on modifiable risk factors including smoking cessation, control of hypertension, dyslipidemia and diabetes as well as appropriate choice of ARV drugs.

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AUTHOR CONTRIBUTIONS

LR, JDL and CS developed the initial analysis protocol. LR performed study co-ordination and prepared the datasets for analysis, CS performed the statistical analysis. CIH prepared the first draft of the manuscript. All authors have provided input at all stages of the project.

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D:A:D Participating Cohorts

Aquitaine	**CPCRA**	**NICE Cohort**
France	**USA**	**France**
ATHENA	**EuroSIDA**	**SHCS**
The Netherlands	**Europe**	**Switzerland**
AHOD	**HIV-BIVUS**	**St.Pierre Brussels Cohort**
Australia	**Sweden**	**Belgium**
BASS	**The ICONA Foundation**	
Spain	**Italy**	

D:A:D Steering Committee: Names marked with *, Chair with #

Members of the D:A:D SC from the Oversight Committee: B. Powderly*, N. Shortman*, C. Moecklinghoff *, G. Reilly*, X. Franquet*

D:A:D Central Coordination: C.I.Hatleberg, L.Ryom, C.A. Sabin*, D. Kamara, C. Smith, A.Phillips*, A. Mocroft, A.Bojesen, J. Nielsen, C. Matthews, D. Raben, J.D. Lundgren#

D:A:D data managers: R. Salbøl Brandt (coordinator), M. Rickenbach, I. Fanti, E. Krum, M. Hillebregt, S .Geffard, Jaohar Mourabi, A. Sundström, M. Delforge, E. Fontas, F. Torres, H. McManus, S. Wright, J. Kjær, Dennis Kristensen

Verification of Endpoints: A. Sjøl (CVD primary endpoint), P. Meidahl (oncology, new endpoint), J. Helweg-Larsen (hematology, new endpoint), J. Schmidt Iversen (nephrology, new endpoint)

Kidney working group: L. Ryom, A. Mocroft, O. Kirk*, P. Reiss*, M. Ross, C.A. Fux, P. Morlat, O. Moranne, A.M. Kesselring, D.A. Kamara, C. Smith, J.D. Lundgren#

Mortality working group: C. Smith, L. Ryom, A. Phillips*, R. Weber* , P. Morlat, C. Pradier*, P. Reiss*, N. Friis-Møller, J. Kowalska, J.D. Lundgren#

Cancer working group: C. Sabin*, M. Law*, A . d'Arminio Monforte*, F. Dabis*, M. Bruyand, P. Reiss*, C. Smith, D.A. Kamara, M Bower, G. Fätkenheuer, A.Grulich, L.Ryom, J.D. Lundgren#

The members of the 11 Cohorts are as follows:

ATHENA (AIDS Therapy Evaluation Project Netherlands):

Central coordination: P. Reiss*, S. Zaheri, M Hillebregt, L.Gras;

Participating physicians (¤Site coordinating physicians): **Academisch Medisch Centrum bij de Universiteit van Amsterdam, Amsterdam:** Prof. dr. J.M. Prins¤, Prof. dr. T.W. Kuijpers, Dr. H.J. Scherpbier, Dr. J.T.M. van der Meer, Dr. F.W.M.N. Wit, Dr. M.H. Godfried, Prof. dr. P. Reiss¤*, Prof. dr. T. van der Poll, Dr. F.J.B. Nellen, Prof. dr. J.M.A. Lange, Dr. S.E. Geerlings, Dr. M. van Vugt, Dr. D. Pajkrt, Drs. J.C. Bos, Drs. M. van der Valk, Drs. M.L. Grijsen, Dr. W.J. Wiersinga, Dr. A. Goorhuis, Dr. J.W.R. Hovius. **Academisch Ziekenhuis Maastricht, Maastricht:** Dr. S. Lowe¤, Dr. A. Oude Lashof, Dr. D. Posthouwer. **Catharina-ziekenhuis, Eindhoven:** Drs. M.J.H. Pronk¤, Dr. H.S.M. Ammerlaan. **Erasmus Medisch Centrum, Rotterdam**: Dr. M.E. van der Ende¤, Dr. T.E.M.S. de Vries-Sluijs, Dr. C.A.M. Schurink, Dr. J.L. Nouwen, Dr. A. Verbon, Drs. B.J.A. Rijnders, Dr. E.C.M. van Gorp, Drs. M. van der Feltz. **Erasmus Medisch Centrum–Sophia, Rotterdam**: Dr. G.J.A. Driessen, Dr. A.M.C. van Rossum. **Flevoziekenhuis. Almere:** Dr. J. Branger¤. **HagaZiekenhuis, Den Haag**: Dr. E.F. Schippers¤, Dr. C. van Nieuwkoop, Drs. E.P. van Elzakker. **Isala Klinieken, Zwolle**: Dr. P.H.P. Groeneveld¤, Drs. J.W. Bouwhuis. **Kennemer Gasthuis:** Drs. R. Soetekouw¤, Prof. dr. R.W. ten Kate. **Leids Universitair Medisch Centrum, Leiden:** Dr. F.P. Kroon¤, Prof. dr. J.T. van Dissel, Dr. S.M. Arend, Dr.

M.G.J. de Boer, Drs. H. Jolink, Dr. H.J.M. ter Vollaard, Drs. M.P. Bauer. **Maasstadziekenhuis, Rotterdam**: Dr. J.G. den Hollander¤, Dr. K. Pogany. **Medisch Centrum Alkmaar, Alkmaar**: Drs. G. van Twillert¤, Drs. W. Kortmann¤, Dr. J.W.T. Cohen Stuart, Dr. B.M.W. Diederen. **Medisch Centrum Haaglanden, Den Haag**: Dr. E.M.S. Leyten¤, Dr. L.B.S. Gelinck. **Medisch Spectrum Twente, Enschede**: Drs. G.J. Kootstra¤, Drs. C.E. Delsing. **Onze Lieve Vrouwe Gasthuis, Amsterdam**: Prof. dr. K. Brinkman¤, Dr. W.L. Blok, Dr. P.H.J. Frissen, Drs. W.E.M. Schouten, Drs. G.E.L. van den Berk. **Sint Elisabeth Ziekenhuis, Tilburg:** Dr. M.E.E. van Kasteren¤, Dr. A.E. Brouwer. **Sint Lucas Andreas Ziekenhuis, Amsterdam**: Dr. J. Veenstra¤, Dr. K.D. Lettinga. **Slotervaartziekenhuis, Amsterdam**: Dr. J.W. Mulder¤, Drs. S.M.E. Vrouenraets, Dr. F.N. Lauw. **Stichting Medisch Centrum Jan van Goyen, Amsterdam:** Drs. A. van Eeden¤, Dr. D.W.M. Verhagen. **Universitair Medisch Centrum Groningen, Groningen:** Drs. H.G. Sprenger¤, Drs. R. Doedens, Dr. E.H. Scholvinck, Dr. S. van Assen, Dr. W.F.W. Bierman. **Universitair Medisch Centrum Sint Radboud, Nijmegen:** Dr. P.P. Koopmans¤, Dr. M. Keuter, Dr. A.J.A.M. van der Ven, Dr. H.J.M. ter Hofstede, Dr. A.S.M. Dofferhoff, Dr. A Warris, Dr. R. van Crevel. **Universitair Medisch Centrum Utrecht, Utrecht**: Prof. dr. A.I.M. Hoepelman¤, Dr. T. Mudrikova, Dr. M.M.E. Schneider, Dr. P.M. Ellerbroek, Dr. J.J. Oosterheert, Dr. J.E. Arends, Dr. M.W.M. Wassenberg, Dr. R.E. Barth. **Vrije Universiteit Amsterdam, Amsterdam**: Dr. M.A. van Agtmael¤, Dr. R.M. Perenboom, Drs. F.A.P. Claessen, Dr. M. Bomers, Dr. E.J.G. Peters. **Wilhelmina Kinderziekenhuis, Utrecht:** Dr. S.P.M. Geelen, Dr. T.F.W. Wolfs, Dr. L.J. Bont. **Ziekenhuis Rijnstate, Arnhem:** Dr. C. Richter¤, Dr. J.P. van der Berg, Dr. E.H. Gisolf. **Admiraal De Ruyter Ziekenhuis, Vlissingen:** Drs. M. van den Berge¤, Drs. A. Stegeman. **Medisch Centrum Leeuwarden, Leeuwarden:** Dr. M.G.A. van Vonderen¤, Drs. D.P.F. van Houte. **Medisch Centrum**

Zuiderzee, Lelystad: Dr. S. Weijer¤, Dr. R. el Moussaoui. **Sint Elisabeth Hospitaal, Willemstad - Curaçao:** Dr. C. Winkel, Drs. F. Muskiet, Drs. Durand, Drs. R. Voigt.

Aquitaine Cohort (France)

Coordination: F. Bonnet, F. Dabis

Scientific committee: F. Bonnet, S. Bouchet, D. Breilh, G. Chêne, F. Dabis, M. Dupon, H. Fleury, V. Gaborieau, D. Lacoste, D. Malvy, P. Mercié, P. Morlat, D. Neau, I. Pellegrin, JL. Pellegrin, S. Reigadas, S. Tchamgoué

Epidemiology and Methodology: M. Bruyand, G. Chêne, F. Dabis, C. Fagard, S. Lawson-Ayayi, L. Richert, R. Thiébaut, L. Wittkop.

Infectious Diseases and Internal Medicine: K. André, F. Bonnet, N. Bernard, L. Caunègre, C. Cazanave, J. Ceccaldi, I. Chossat, C. Courtault, FA. Dauchy, S. De Witte, D. Dondia, M. Dupon, A. Dupont, P. Duffau, H. Dutronc, S. Farbos, I. Faure, V. Gaborieau, Y. Gerard, C. Greib, M. Hessamfar-Joseph, Y. Imbert, D. Lacoste, P. Lataste, E. Lazaro, D. Malvy, J. Marie, M. Mechain, JP. Meraud, P. Mercié, E. Monlun, P. Morlat, D. Neau, A. Ochoa, JL. Pellegrin, M. Pillot-Debelleix, T. Pistone, I. Raymond, MC. Receveur, P. Rispal, L. Sorin, S. Tchamgoué, C. Valette, MA. Vandenhende, MO. Vareil, JF. Viallard, H. Wille, G. Wirth.

Immunology: JF. Moreau, I. Pellegrin.

Virology: H. Fleury, ME. Lafon, S. Reigadas, P. Trimoulet.

Pharmacology: S. Bouchet, D. Breilh, F. Haramburu, G. Miremont-Salamé

Data collection, Project Management and Statistical Analyses: MJ. Blaizeau, I. Crespel, M. Decoin, S. Delveaux, F. Diarra, C. D'Ivernois, C. Hanappier, D. Lacoste, S. Lawson-Ayayi, O. Leleux, F. Le Marec, E. Lenaud, J. Mourali, E. Pernot, A. Pougetoux, B. Uwamaliya-Nziyumvira, A. Tsaranazy, A. Valdes.

IT department and eCRF development: V. Conte, I. Louis, G. Palmer, V. Sapparrart, D. Touchard.

AHOD (Australian HIV Observational Database, Australia):

Central coordination: M. Law *, K. Petoumenos, H. McManus, S. Wright, C. Bendall (Sydney, New South Wales);

Participating physicians (city, state): R. Moore, S. Edwards, J. Hoy, K. Watson, N. Roth, J. Nicholson (Melbourne, Victoria); M Bloch, T. Franic, D. Baker, R. Vale, A. Carr, D. Cooper (Sydney, New South Wales); J. Chuah, M. Ngieng (Gold Coast, Queensland), D. Nolan, J. Skett (Perth, Western Australia).

BASS (Spain):

Central coordination: G. Calvo, F. Torres, S. Mateu (Barcelona);

Participating physicians (city): P. Domingo, M.A. Sambeat, J. Gatell, E. Del Cacho, J. Cadafalch, M. Fuster (Barcelona); C. Codina, G. Sirera, A. Vaqué (Badalona).

The Brussels St Pierre Cohort (Belgium):

Coordination: S. De Wit*, N. Clumeck, M. Delforge, C. Necsoi. Participating physicians: N. Clumeck, S. De Wit*, AF Gennotte, M. Gerard, K. Kabeya, D. Konopnicki, A. Libois, C. Martin, M.C. Payen, P. Semaille, Y. Van Laethem.

CPCRA (USA):

Central coordination: J. Neaton, G. Bartsch, W.M. El-Sadr*, E. Krum, G. Thompson, D. Wentworth;

Participating physicians (city, state): R. Luskin-Hawk (Chicago, Illinois); E. Telzak (Bronx, New York); W.M. El-Sadr (Harlem, New York); D.I. Abrams (San Francisco, California); D. Cohn (Denver, Colorado); N. Markowitz (Detroit, Michigan); R. Arduino (Houston, Texas);

D. Mushatt (New Orleans, Louisiana); G. Friedland (New Haven, Connecticut); G. Perez (Newark, New Jersey); E. Tedaldi (Philadelphia, Pennsylvania); E. Fisher (Richmond, Virginia); F. Gordin (Washington, DC); L.R. Crane (Detroit, Michigan); J. Sampson (Portland, Oregon); J. Baxter (Camden, New Jersey).

EuroSIDA (multinational**)**

Coordinating Centre: J Lundgren#, O Kirk*, A Mocroft, A Cozzi-Lepri, D Grint, D Podlekareva, J Kjær, L Peters, J Reekie, J Kowalska, J Tverland, A H Fischer, J Nielsen

Participating countries and physicians Argentina: (M Losso), C Elias, Hospital JM Ramos Mejia, Buenos Aires.

Austria: (N Vetter), Pulmologisches Zentrum der Stadt Wien, Vienna; R Zangerle, Medical University Innsbruck, Innsbruck.

Belarus: (I Karpov), A Vassilenko, Belarus State Medical University, Minsk, VM Mitsura, Gomel State Medical University, Gomel; O Suetnov, Regional AIDS Centre, Svetlogorsk.

Belgium: (N Clumeck), S De Wit*, M Delforge, Saint-Pierre Hospital, Brussels; R Colebunders, Institute of Tropical Medicine, Antwerp; L Vandekerckhove, University Ziekenhuis Gent, Gent.

Bosnia-Herzegovina: (V Hadziosmanovic), Klinicki Centar Univerziteta Sarajevo, Sarajevo.

Bulgaria: (K Kostov), Infectious Diseases Hospital, Sofia.

Croatia: (J Begovac), University Hospital of Infectious Diseases, Zagreb.

Czech Republic: (L Machala), D Jilich, Faculty Hospital Bulovka, Prague; D Sedlacek, Charles University Hospital, Plzen.

Denmark: (J Nielsen), G Kronborg,T Benfield, M Larsen, Hvidovre Hospital, Copenhagen; J Gerstoft, T Katzenstein, A-B E Hansen, P Skinhøj, Rigshospitalet, Copenhagen; C Pedersen, Odense University Hospital, Odense; L Ostergaard, Skejby Hospital, Aarhus.

Estonia: (K Zilmer), West-Tallinn Central Hospital, Tallinn; Jelena Smidt, Nakkusosakond Siseklinik, Kohtla-Järve.

Finland: (M Ristola), Helsinki University Central Hospital, Helsinki.

France: (C Katlama), Hôpital de la Pitié-Salpétière, Paris; J-P Viard, Hôpital Necker-Enfants Malades, Paris; P-M Girard, Hospital Saint-Antoine, Paris; JM Livrozet, Hôpital Edouard Herriot, Lyon; P Vanhems, University Claude Bernard, Lyon; C Pradier, Hôpital de l'Archet, Nice; F Dabis*, D Neau, Unité INSERM, Bordeaux.

Germany: (J Rockstroh), Universitäts Klinik Bonn; R Schmidt, Medizinische Hochschule Hannover; J van Lunzen, O Degen, University Medical Center Hamburg-Eppendorf, Infectious Diseases Unit, Hamburg; HJ Stellbrink, IPM Study Center, Hamburg; S Staszewski, JW Goethe University Hospital, Frankfurt; Markus Bickel, Medizinische Poliklinik, Munich; G. Fätkenheuer, Universität Köln, Cologne.

Greece: (J Kosmidis), P Gargalianos, G Xylomenos, J Perdios, Athens General Hospital; G Panos, A Filandras, E Karabatsaki, 1st IKA Hospital; H Sambatakou, Ippokration Genereal Hospital, Athens.

Hungary: (D Banhegyi), Szent Lásló Hospital, Budapest.

Ireland: (F Mulcahy), St. James's Hospital, Dublin.

Israel: (I Yust), D Turner, M Burke, Ichilov Hospital, Tel Aviv; S Pollack, G Hassoun, Rambam Medical Center, Haifa; S Maayan, Hadassah University Hospital, Jerusalem.

Italy: (S Vella), Istituto Superiore di Sanità, Rome; R Esposito, I Mazeu, C Mussini, Università Modena, Modena; C Arici, Ospedale Riuniti, Bergamo; R Pristera, Ospedale Generale Regionale, Bolzano; F Mazzotta, A Gabbuti, Ospedale S Maria Annunziata, Firenze; V Vullo, M Lichtner, University di Roma la Sapienza, Rome; A Chirianni, E Montesarchio, M Gargiulo, Presidio Ospedaliero AD Cotugno, Monaldi Hospital, Napoli; G Antonucci, A Testa, P Narciso, C Vlassi, M Zaccarelli, Istituto Nazionale Malattie Infettive

Lazzaro Spallanzani, Rome; A Lazzarin, A Castagna, N Gianotti, Ospedale San Raffaele, Milan; M Galli, A Ridolfo, Osp. L. Sacco, Milan; A d'Arminio Monforte*, Istituto Di Clinica Malattie Infettive e Tropicale, Milan.

Latvia: (B Rozentale), I Zeltina, Infectology Centre of Latvia, Riga.

Lithuania: (S Chaplinskas), Lithuanian AIDS Centre, Vilnius.

Luxembourg: (R Hemmer), T Staub, Centre Hospitalier, Luxembourg.

Netherlands: (P Reiss*), Academisch Medisch Centrum bij de Universiteit van Amsterdam, Amsterdam.

Norway: (V Ormaasen), A Maeland, J Bruun, Ullevål Hospital, Oslo.

Poland: (B Knysz) J Gasiorowski, Medical University, Wroclaw; A Horban, E Bakowska, Centrum Diagnostyki i Terapii AIDS, Warsaw; A Grzeszczuk, R Flisiak, Medical University, Bialystok; A Boron-Kaczmarska, M Pynka, M Parczewski, Medical Univesity, Szczecin; M Beniowski, E Mularska, Osrodek Diagnostyki i Terapii AIDS, Chorzow; H Trocha, Medical University, Gdansk; E Jablonowska, E Malolepsza, K Wojcik, Wojewodzki Szpital Specjalistyczny, Lodz.

Portugal: (F Antunes), M Doroana, L Caldeira, Hospital Santa Maria, Lisbon; K Mansinho, Hospital de Egas Moniz, Lisbon; F Maltez, Hospital Curry Cabral, Lisbon.

Romania: (D Duiculescu), Spitalul de Boli Infectioase si Tropicale: Dr. Victor Babes, Bucarest.

Russia: (A Rakhmanova), Medical Academy Botkin Hospital, St Petersburg; N Zakharova, St Petersburg AIDS Centre, St Peterburg; S Buzunova, Novgorod Centre for AIDS, Novgorod.

Serbia: (D Jevtovic), The Institute for Infectious and Tropical Diseases, Belgrade.

Slovakia: (M Mokráš), D Staneková, Dérer Hospital, Bratislava.

Slovenia: (J Tomazic), University Clinical Centre Ljubljana, Ljubljana.

Spain: (J González-Lahoz), V Soriano, P Labarga, J Medrano, Hospital Carlos III, Madrid; S Moreno, JM Rodriguez, Hospital Ramon y Cajal, Madrid; B Clotet, A Jou, R Paredes, C Tural, J Puig, I Bravo, Hospital Germans Trias i Pujol, Badalona; JM Gatell, JM Miró, Hospital Clinic i Provincial, Barcelona; P Domingo, M Gutierrez, G Mateo, MA Sambeat, Hospital Sant Pau, Barcelona.

Sweden: (A Karlsson), Venhaelsan-Sodersjukhuset, Stockholm; L Flamholc, Malmö University Hospital, Malmö.

Switzerland: (B Ledergerber), R Weber*, University Hospital, Zürich; P Francioli, M Cavassini, Centre Hospitalier Universitaire Vaudois, Lausanne; B Hirschel, E Boffi, Hospital Cantonal Universitaire de Geneve, Geneve; H Furrer, Inselspital Bern, Bern; M Battegay, L Elzi, University Hospital Basel.

Ukraine: (E Kravchenko), N Chentsova, Kiev Centre for AIDS, Kiev; V Frolov, G Kutsyna, Luhansk State Medical University; Luhansk; S Servitskiy, Odessa Region AIDS Center, Odessa; M Krasnov, Kharkov State Medical University, Kharkov.

United Kingdom: (S Barton), St. Stephen's Clinic, Chelsea and Westminster Hospital, London; AM Johnson, D Mercey, Royal Free and University College London Medical School, London (University College Campus); A Phillips, MA Johnson, A Mocroft, Royal Free and University College Medical School, London (Royal Free Campus); M Murphy, Medical College of Saint Bartholomew's Hospital, London; J Weber, G Scullard, Imperial College School of Medicine at St. Mary's, London; M Fisher, Royal Sussex County Hospital, Brighton; C Leen, Western General Hospital, Edinburgh.

HivBivus (Sweden):

Central coordination: L. Morfeldt, G. Thulin, A. Sundström.

Participating physicians (city): B. Åkerlund (Huddinge); K. Koppel, A. Karlsson (Stockholm); L. Flamholc, C. Håkangård (Malmö).

The ICONA Foundation (Italy):

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Scientific secretary: A d'Arminio Monforte, A Antinori, A Castagna, F Ceccherini-Silberstein, A Cozzi-Lepri, E Girardi, S Lo Caputo, C Mussini, M Puoti

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Statistical and monitoring team: A Cozzi-Lepri, I Fanti, L Galli, P Lorenzini, A Rodano, M Shanyinde, A Tavelli

Participating physicians and centres: A Giacometti, A Costantini, S Mazzoccato (Ancona); G Angarano, L Monno, C Santoro (Bari); F Maggiolo, C Suardi (Bergamo); P Viale, E Vanino, G Verucchi (Bologna); F Castelli, E Quiros Roldan, C Minardi (Brescia); T Quirino, C Abeli (Busto Arsizio); PE Manconi, P Piano (Cagliari); J Vecchiet, K Falasca (Chieti); L Sighinolfi, D Segala (Ferrara); F Mazzotta, S Lo Caputo (Firenze); G Cassola, C Viscoli, A Alessandrini, R Piscopo, G Mazzarello (Genova); C Mastroianni, V Belvisi (Latina); P Bonfanti, I Caramma (Lecco); A Chiodera, AP Castelli (Macerata); M Galli, A

Lazzarin, G Rizzardini, M Puoti, A d'Arminio Monforte, AL Ridolfo, R Piolini, A Castagna, S Salpietro, L Carenzi, MC Moioli, C Tincati, G. Marchetti (Milano); C Mussini, C Puzzolante (Modena); A Gori, G Lapadula (Monza); N Abrescia, A Chirianni, G Borgia, F Di Martino, L Maddaloni, I Gentile, R Orlando (Napoli); F Baldelli, D Francisci (Perugia); G Parruti, T Ursini (Pescara); G Magnani, MA Ursitti (Reggio Emilia); R Cauda, M Andreoni, A Antinori, V Vullo, A Cingolani, G Baldin, L Gallo, E Nicastri, R Acinapura, M Capozzi, R Libertone, S Savinelli, M Zaccarelli (Roma); M Cecchetto, F Viviani (Rovigo); MS Mura, G Madeddu (Sassari); A De Luca, B Rossetti (Siena); P Caramello, G Di Perri, GC Orofino, S Bonora, M Sciandra (Torino); M Bassetti, A Londero (Udine); G Pellizzer, V Manfrin (Vicenza).

Nice HIV Cohort (France):

Central coordination: C. Pradier*, E. Fontas, K. Dollet, C. Caissotti.

Participating physicians: P. Dellamonica, E. Bernard, E. Cua, F. De Salvador-Guillouet, J. Durant, S. Ferrando, V. Mondain-Miton, A. Naqvi, I. Perbost, B. Prouvost-Keller, S. Pillet, P. Pugliese, V. Rahelinirina, P.M. Roger.

SHCS (Swiss HIV Cohort Study, Switzerland):

V Aubert, M Battegay, E Bernasconi, J Böni, HC Bucher, C Burton-Jeangros, A Calmy, M Cavassini, G Dollenmaier, M Egger, L Elzi, J Fehr, J Fellay, H Furrer (Chairman of the Clinical and Laboratory Committee), CA Fux, M Gorgievski, H Günthard (President of the SHCS), D Haerry (deputy of "Positive Council"), B Hasse, HH Hirsch, M Hoffmann, I Hösli, C Kahlert, L Kaiser, O Keiser, T Klimkait, R Kouyos, H Kovari, B Ledergerber, G Martinetti, B Martinez de Tejada, K Metzner, N Müller, D Nadal, D Nicca, G Pantaleo, A Rauch (Chairman of the Scientific Board), S Regenass, M Rickenbach (Head of Data Center),

C Rudin (Chairman of the Mother & Child Substudy), F Schöni-Affolter, P Schmid, J Schüpbach, R Speck, P Tarr, A Telenti, A Trkola, P Vernazza, R Weber*, S Yerly.

FIGURE LEGENDS

Figure 1: Use of invasive procedures and drug interventions before and in the first month after MI, stratified by calendar period

ACE-inhibitors indicate angiotensin converting enzyme-inhibitors; MI, myocardial infarction *Angioplasty, coronary bypass, endarterectomy

Figure 2: Causes of death among study participants dying following myocardial infarction

a) Overall, stratified by timing of death relative to MI, b) Overall, stratified by calendar period

AIDS/HIV indicates acquired immunodeficiency syndrome/human immunodeficiency virus; CVDs, cardiovascular diseases; MI, myocardial infarction. *Suicide, psychiatric disease, drug overdose, accident/violent death, non-bacterial infections, pancreatitis, renal failure, gastrointestinal disease, complications due to diabetes, other known/unknown causes †Chronic viral hepatitis B and/or C and liver failure, ‡Other cardiovascular diseases

Table 1: Characteristics of individuals at time of myocardial infarction

Demographic characteristics		**Overall**	**Calendar period**					
			1999-2002	**2003-2004**	**2005-2006**	**2007-2008**	**2009-2010**	**2011-2014**
Number of MIs		1008	214	191	153	174	122	154
Dundee classification								
	Definite	634 (62.9)	126 (58.9)	125 (65.5)	101 (66.0)	108 (62.1)	81 (66.4)	93 (60.4)
	Possible	213 (21.1)	45 (21.0)	35 (18.3)	38 (24.8)	47 (27.0)	28 (23.0)	20 (13.0)
	Unclassifiable	161 (16.0)	43 (20.1)	31 (16.2)	14 (9.2)	19 (10.9)	13 (10.7)	41 (26.6)
Male gender		915 (90.8)	194 (90.7)	177 (92.7)	137 (89.5)	154 (88.5)	114 (93.4)	139 (90.3)
Age (years)	Median	51	48	49	49	52	51	54
	(IQR)	(44, 58)	(42, 55)	(42, 58)	(43, 58)	(45, 59)	(46, 58)	(48, 62)

Race								
	White	563 (55.9)	146 (68.2)	100 (52.4)	75 (49.0)	94 (54.0)	66 (54.1)	82 (53.3)
	Black African	36 (3.6)	13 (6.1)	10 (5.2)	7 (4.6)	3 (1.7)	1 (0.8)	2 (1.3)
	Other/Unknown	409 (40.6)	55 (5.5)	81 (8.0)	71 (7.0)	77 (7.6)	46 (4.6)	69 (6.8)
Mode of HIV-acquisition								
	IDU	149 (14.8)	39 (18.2)	29 (15.2)	20 (13.1)	26 (14.9)	15 (12.3)	20 (13.0)
	MSM	580 (57.5)	115 (53.7)	119 (62.3)	85 (55.6)	96 (55.2)	72 (59.0)	93 (60.4)
	Heterosexual	219 (21.7)	47 (22.0)	29 (15.2)	20 (13.1)	26 (14.9)	15 (12.3)	20 (13.0)
	Other/Unknown	60 (6.0)	13 (6.1)	14 (7.3)	9 (5.9)	9 (5.2)	6 (4.9)	9 (5.8)
HIV-related characteristics								
AIDS		390 (38.6)	80 (37.4)	68 (35.6)	62 (40.5)	70 (40.2)	52 (42.6)	58 (37.7)

Median CD4 (cells/mm^3)	Median (IQR)	480 (316, 703)	398 (244, 620)	441 (300, 627)	460 (320, 704)	438 (270, 632)	587 (400, 770)	585 (401, 856)
HIV RNA (<50 copies/ml)		656 (65.3)	95 (44.6)	107 (56.0)	104 (68.0)	128 (74.0)	95 (78.5)	127 (82.5)
Currently on ARVs		911 (90.4)	184 (86.0)	173 (90.6)	137 (89.5)	153 (87.9)	116 (95.1)	148 (96.1)
ARV naïve		27 (2.7)	5 (2.3)	3 (1.6)	2 (1.3)	10 (5.8)	3 (2.5)	4 (2.6)
Ever received NRTIs		980 (97.2)	209 (97.7)	187 (97.9)	151 (98.7)	164 (94.3)	119 (97.5)	150 (97.4)
Cumulative exposure (years) -NRTIs	Median (IQR)	7.8 (4.9,11.3)	5.0 (3.5, 7.0)	7.4 (5.6, 9.0)	8.5 (5.2, 10.5)	9.4 (5.5, 11.8)	11.0 (6.7, 13.9)	12.6 (7.0, 15.9)
Ever received NNRTIs		696 (69.1)	127 (59.4)	124 (64.9)	109 (71.2)	127 (73.0)	91 (74.6)	118 (76.6)

Cumulative exposure (years) -NNRTIs	Median (IQR)	2.7 (1.1, 4.8)	1.5 (0.7, 2.4)	2.8 (1.4, 4.0)	2.8 (1.0, 4.2)	3.2 (1.2, 5.9)	3.5 (1.6, 7.2)	6.2 (1.5, 10.7)
Ever received PIs		862 (85.5)	191 (89.3)	168 (88.0)	131 (85.6)	144 (82.8)	103 (84.4)	125 (81.2)
Cumulative exposure (years) -PIs	Median (IQR)	4.4 (2.6, 6.9)	3.3 (2.3, 4.3)	4.6 (2.8, 6.3)	5.0 (2.7, 7.3)	5.4 (2.9, 8.8)	5.6 (2.6, 10.4)	6.5 (3.4, 11.0)
CVD-related characteristics								
Smoking								
	Current	537 (53.3)	106 (49.5)	92 (48.2)	82 (53.6)	101 (58.1)	72 (59.0)	84 (54.6)
	Ex-smoker	242 (24.0)	50 (23.4)	40 (20.9)	36 (23.5)	47 (27.0)	27 (22.1)	42 (27.3)
	Never	115 (11.4)	19 (8.9)	25 (13.1)	22 (14.4)	19 (10.9)	17 (13.9)	13 (8.4)
	Unknown	114 (11.3)	39 (18.2)	34 (17.8)	13 (8.5)	7 (4.0)	6 (4.9)	15 (9.7)

Family history of CVD		137 (13.6)	31 (14.5)	27 (14.1)	22 (14.4)	23 (13.2)	16 (13.1)	18 (11.7)
Framingham risk score >10-20%		586 (58.2)	105 (49.5)	101 (52.9)	87 (56.8)	102 (58.6)	84 (68.9)	107 (79.5)
BMI (kg/m2)								
	<18	36 (3.6)	5 (2.3)	7 (3.7)	2 (1.3)	10 (5.8)	7 (5.7)	5 (3.3)
	≥18 ≤26	495 (49.1)	115 (53.7)	100 (52.4)	79 (51.6)	76 (43.7)	52 (42.6)	73 (47.4)
	>26 ≤30	129 (12.8)	24 (11.2)	21 (11.0)	20 (13.1)	19 (10.9)	21 (17.2)	24 (15.6)
	>30	51 (5.1)	11 (5.1)	11 (5.8)	11 (7.2)	10 (5.8)	2 (1.6)	6 (3.9)
	Unknown	297 (29.5)	59 (27.6)	52 (27.2)	41 (26.8)	59 (33.9)	40 (32.8)	46 (29.9)
Prior diabetes		144 (14.3)	34 (15.9)	31 (16.2)	23 (15.0)	22 (12.6)	10 (8.2)	24 (15.6)
Prior stroke		42 (4.2)	12 (5.6)	7 (3.7)	6 (3.9)	6 (3.5)	3 (2.5)	8 (5.2)
Prior MI		78 (7.7)	26 (12.2)	16 (8.4)	10 (6.5)	11 (6.3)	5 (4.1)	10 (6.5)
Dyslipidemia[a]		671 (66.6)	123 (57.5)	134 (70.2)	94 (61.4)	120 (69.0)	93 (76.2)	107 (69.5)

Hypertension[b]		428 (42.5)	64 (29.9)	73 (38.2)	60 (39.2)	80 (45.0)	63 (51.6)	88 (57.1)
TC (mmol/l)	Median (IQR)	5.6 (4.7, 6.5)	5.7 (4.7, 6.7)	5.8 (4.8, 6.7)	5.5 (4.7, 6.3)	5.5 (4.7, 6.3)	5.8 (5.0, 6.6)	5.3 (4.5, 6.2)
HDL-C (mmol/l)	Median (IQR)	1.1 (0.9, 1.3)	1.0 (0.8, 1.2)	1.1 (0.8, 1.3)	1.1 (0.9, 1.3)	1.1 (0.9, 1.4)	1.1 (0.9, 1.3)	1.1 (0.9, 1.4)
Triglycerides (mmol/l)	Median (IQR)	2.2 (1.4, 3.6)	2.4 (1.5, 3.9)	2.4 (1.4, 4.4)	2.2 (1.5, 4.1)	2.1 (1.4, 3.1)	2.3 (1.6, 3.6)	1.9 (1.2, 3.0)

HIV, human immunodeficiency virus; MI, myocardial infarction; IDU, intravenous drug use; MSM, men who have sex with men; AIDS, acquired immunodeficiency syndrome; ARVs, anti-retroviral drugs; NRTIs, nucleoside reverse transcriptase inhibitors; NNRTIs, non-nucleoside reverse transcriptase inhibitors; PIs, protease inhibitors; CVD, cardiovascular disease; BMI, body mass index; TC, total cholesterol; HDL-C, high density lipoprotein cholesterol. [a]TC $\geq$6.2 mmol/L, HDL-C$\leq$0.9 mmol/L, TC:HDL-C ratio $\geq$6.5 or receipt of lipid-lowering drugs. [b]Systolic blood pressure >140 mm Hg, diastolic blood pressure > 90 mm Hg or receipt of anti-hypertensives/angiotensin converting enzyme-inhibitors.

Figure 1. Use of invasive procedures and drug interventions before and in the first month after MI, stratified by calendar period

Figure 2. Causes of death among study participants dying following myocardial infarction

a) Overall, stratified by timing of death relative to MI

b) Overall, stratified by calendar period

Table 2: Factors associated with mortality following myocardial infarction, conditioned on the fact that patient survives for at least one month – multivariable model *

Factor	**Excluding interventions in first month**	**Including interventions in first month**
	Hazard rate (95% CI), p-value	**Hazard rate (95% CI), p-value**
Age (/10 years older)	1.18 (1.09, 1.28) p=0.0001	1.13 (1.05, 1.23) p=0.002
AIDS	1.45 (1.05, 2.01) p=0.02	1.42 (1.02, 1.98) p=0.04
CD4 count (/50 cells/mm^3 increment)	0.97 (0.94, 1.00) p=0.05	0.96 (0.93, 1.00) p=0.03
HIV RNA (/$\log_{10}$ increment)	1.19 (1.03, 1.38) p=0.0001	1.19 (1.02, 1.38) p=0.03
Previous MI	1.85 (1.14, 3.00) p=0.02	1.63 (1.00, 2.67) p=0.05
Previous diabetes	2.16 (1.46, 3.19) p=0.01	2.13 (1.43, 3.16) p=0.0002
Year of MI (/ later year)	0.95 (0.89, 1.00) p=0.007	0.98 (0.92, 1.04) p=0.50
Interventions in first month		
Anti-platelets	n/a	0.72 (0.44, 1.17) p=0.18

ACE- Inhibitors	n/a	1.07 (0.65, 1.76) p=0.80
Anti-hypertensives	n/a	0.76 (0.45, 1.29) p=0.31
Lipid-lowering drugs	n/a	0.93 (0.58, 1.49) p=0.76
ICPs	n/a	0.44 (0.31, 0.63) p=0.0001

AIDS indicates acquired immunodeficiency syndrome; MI, myocardial infarction; ACE-inhibitors, angiotensin converting enzyme- inhibitors; ICP, invasive cardiovascular procedures *Also adjusted for cohort.

Table 3: Factors associated with short-term mortality following myocardial infarction – multivariable model*

Factor	**No adjustment for interventions in first month**	**Adjustment for interventions in first month**
	Odds ratio (95% CI), p-value	**Odds ratio (95% CI), p-value**
IDU	1.90 (1.20, 2.99) p=0.006	1.66 (0.98, 2.83) p=0.06
CD4 count (/50 cells/mm^3 increment)	0.93 (0.90, 0.96) p=0.0001	0.92 (0.89, 0.96) p=0.0001
Family history of CVD	0.46 (0.25, 0.86) p=0.01	0.61 (0.30, 1.24) p=0.17
Stroke	3.24 (1.61, 6.53) p=0.001	2.08 (0.90, 4.84) p=0.09
Year of MI (/later year)	0.88 (0.83, 0.93) p=0.0001	0.97 (0.91, 1.02) p=0.23
Interventions in first month		
Anti-platelets	n/a	0.09 (0.03, 0.31) p=0.0001
ACE- inhibitors	n/a	0.45 (0.12, 1.66)

		p=0.23
Anti-hypertensives	n/a	0.25 (0.05, 1.18) p=0.08
Lipid-lowering drugs	n/a	0.27 (0.08, 0.95) p=0.04
ICPs	n/a	0.07 (0.04, 0.13) p=0.0001

IDU indicates intravenous drug use; CVD, cardiovascular disease; MI, myocardial infarction; ACE-inhibitors, angiotensin converting enzyme- inhibitors; ICP, invasive cardiovascular procedures *Also adjusted for cohort.